I. REMARKS

Claims 2-13 and 15-30 are pending in the application. Claim 28 has been withdrawn from consideration as being directed to non-elected subject matter. Claims 2-13, 15-27 and 29-30 stand rejected.

A. Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 2-13, 15-27 and 29-30 have been rejected under 35 U.S.C. § 112, second paragraph as being indefinite. The present amendments changes the dependency of claims 2-13 and 16-17 from claim 30 to claim 29, thereby overcoming the rejection of these claims as vague and indefinite due to improper dependency.

Claim 2 has been rejected as vague and indefinite in that the metes and bounds of the phrase "...which does not exhibit any reversion to the wild type..." is asserted to be unclear. Claim 2 has been amended to recite conditions whereby the required rate of reversion to wild type can be measured. Support for this amendment is found in the Specification at page 6, lines 18-32.

Claim 6 has been amended to correct the defect noted by the examiner, replacing the phrase "HSV-1 mutant 1802" with the phrase --HSV-1 strain 1802--.

Claim 7 has been rejected as vague and indefinite in that the metes and bounds of the phrase "a mutant which is completely or partially replication-deficient" are asserted to be unclear . Applicant respectfully directs the examiner's attention to the specification at page 7, last paragraph, through page 8, first paragraph, where the term in question is discussed at length, with citation to examples, and defined as meaning either completely replication-deficient, or at least severely impaired in its ability to produce progeny virus (e.g., by several orders of magnitude). Applicants submit that in light of this definition in the specification, claim 7 is as clear and precise as the subject matter permits and, read in light of the specification, clearly defines the

metes and bounds of the subject matter claimed. Applicants therefore respectfully request that this rejection be reconsidered and withdrawn.

Claim 10 has been rejected as vague and indefinite in that the metes and bounds of the term "stably integrated" are unclear. Applicants respectfully submit that this is a term of art that is readily understood by persons having ordinary skill in the art as meaning that due to the DNA integration into the herpesvirus genome, the transgene sequence will not be lost upon serial viral passage (i.e., the transgene becomes a part of the transmissible viral genome). Furthermore, in the Specification at page 6, lines 18-32, there is a detailed discussion of genetic stability as it relates specifically to the present invention. Applicants therefore respectfully submit that the language of the claim is as clear as the subject matter permits, and is in compliance with §112, second paragraph.

Claims 12-13 and 21-22 have been rejected as vague and indefinite in that the metes and bounds of the phrase "... wherein use is made of ..." virus are unclear.

Claim 18 has been rejected as vague and indefinite in that the metes and bounds of the words "based on" are unclear. Applicant believes that the present amendments to claim 18 make it clear that the vector is an AAV vector.

Claim 24 has been rejected as vague and indefinite in that the phrase "the vector" lacks a clear antecedent basis. The present amendment to claim 24 is believed to remove this defect.

Claims 29-30 have been rejected as vague and indefinite in that the metes and bounds of the phrase "a rep and a cap gene derived from" are unclear. The claims have been amended as suggested by the examiner, thereby removing this asserted ambiguity.

In view of the foregoing amendments and remarks, Applicants respectfully submit that the present claims meet all the requirements of 35 U.S.C. § 112, second paragraph. Applicants therefore request that the rejections of the claims under this section be withdrawn.

B. Rejections under 35 U.S.C. § 102(b)

The Patent Office has rejected claims 2-5, 7-13, 15-27 and 29-30 as being anticipated under §102(b) by Dong et al. (WO 95/06743). The Patent Office asserts that Dong et al. teach the construction of helper viruses for production of rAAV which comprise genes essential for AAV replication, that the helper viruses can be obtained from adenovirus or from one of several viruses classified as "herpesvirus," that the helper virus can be either replication competent or replication defective, that such helper viruses will contain one or more rep, lip or cap genes, the deletion of essential and non-essential genes from the helper virus genome, and that expression of essential AAV genes can be achieved with either their natural promoters or with heterologous promoters. The Patent Office notes a prophetic example in Dong, et al. that is alleged to teach insertion of AAV rep, lip and/or cap sequences into the genome of HSV.

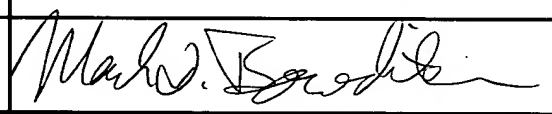
Applicants respectfully traverse this rejection. The Dong reference only discloses examples of recombinant adenoviruses. There are no experiments on HSV or other herpesvirus, as recited in the present claims. The reference only teaches the general idea that it should be possible to produce recombinant herpesviruses expression AAV rep and cap genes, and those which carry AAV vectors as transgenes. As evidence in support of their suggestion, Dong et al. point to two papers published in 1980, which describe for the first time homologous recombination in the HSV genome. "Gene modification" is achieved by homologous DNA recombination after cotransfection of HSV DNA and cloned HSV DNA fragments carrying the modified HSV gene, flanked by HSV sequences, by which homologous recombination in cells is to take place. The

fact that the supporting reference cited was fifteen years old at the time of the filing of the Dong application demonstrates that it represents only a general hint that recombinant viruses (including herpesvirus) can be generated by homologous recombination. Dong, et al. merely specified the commonly-used AAV vectors for use in the system suggested by the 1980 reference. As the present application makes clear, there were considerable obstacles to overcome before the presently claimed invention could be achieved, and therefore absent some demonstration that the contemplated viruses are genetically stable, that the transgenes are expressed at an acceptable level with the required regulation, and that the desired packing of AAV vector DNA occurs, both the Dong reference and the 1980 reference upon which it relies cannot be considered as enabling. See, generally, Specification at page 4, lines 18-30. In fact, as the present application indicates, previous attempts at a system for replicating and packaging AAVs using herpesvirus amplicons met with failure due to the loss of the amplicons after only a few passages. See, Specification at page 3, line 22 - page 4, line 8.

Because Dong, et al. is not enabling for the presently-claimed invention, and does not in fact adequately describe methods for obtaining the claimed modified recombinant herpesvirus, Dong, et al. cannot anticipate the present claims. Applicants respectfully request reconsideration and withdrawal of this rejection.

II. CONCLUSION

In view of the foregoing, Applicants respectfully submit that the present claims are in condition for allowance, and request that the pending rejections be withdrawn. Favorable action on the claims is earnestly solicited.

RESPECTFULLY SUBMITTED,					
NAME AND REG. NUMBER	Mark I. Bowditch, Reg. No. 40,315				
SIGNATURE			DATE	2/24/03	
Address	Rothwell, Figg, Ernst & Manbeck 1425 K Street, N.W., Suite 800				
City	Washington	*State*	D.C.	*Zip Code*	20005
Country	U.S.A.	*Telephone*	202-783-6040	*Fax*	202-783-6031

Attachments: Marked-Up Copies of Amendments

2923-104.amd.wpd

Amended Claims: Version with markings to show changes made

2. (twice amended) A recombinant herpesvirus as claimed in claim ~~30~~ 29, ~~which does not exhibit any reversion to the wild type~~ wherein after three dilution steps in a plaque purification no visible reversion to the wild type is observed.

3. (twice amended) A recombinant herpesvirus as claimed in claim ~~30~~ 29, which additionally comprises a reporter gene.

4. (twice amended) A recombinant herpesvirus as claimed in claim ~~30~~ 29, which is selected from the group of Herpesviridae comprising herpes simplex virus (HSV), cytomegalovirus (CMV), pseudorabies virus (PRV) and Epstein-Barr virus (EBV) and other members of the herpesvirus family.

6. (amended) A recombinant herpesvirus as claimed in claim 5, which is the HSV-1 ~~mutant~~ strain 1802.

7. (twice amended) A recombinant herpesvirus as claimed in claim ~~30~~ 29, which is a mutant which is completely or partially replication-deficient.

8. (twice amended) A recombinant herpesvirus as claimed in claim ~~30~~ 29, wherein the insertion does not encompass the complete AAV ITR sequence.

9. (twice amended) A recombinant herpesvirus as claimed in claim ~~30~~ 29, wherein the AAV rep gene and the AAV cap gene are inserted in the U_L or the U_L region of the herpesvirus.

10. (twice amended) A recombinant herpesvirus as claimed in claim ~~30~~ 29, wherein the AAV rep gene and the AAV cap gene are stably integrated into the genome of the herpesvirus.

12. (amended) The process as claimed in claim 10 or 11, wherein ~~use is made of~~ the herpesvirus is an HSV mutant which possesses a unique restriction site.

13. (amended) The process as claimed in claim 11, wherein ~~use is made of~~ the herpesvirus is an HSV mutant which is completely or partially replication-deficient.

15. (twice amended) A vector, which comprises a nucleic acid as claimed in claim ~~31~~ 30.

16. (twice amended) A viral composition which comprises a recombinant herpesvirus as claimed in claim ~~30~~ 29.

18. (twice amended) A process for preparing infectious AAV vector preparations, comprising the steps of:

a) preparing a viral vector which is ~~based on adeno-associated viruses (AAVs)~~ an adeno-associated virus (AAV) vector

b) preparing a recombinant herpesvirus as claimed in claim ~~30~~ 29

c) introducing the AAV vector from (a) and the recombinant herpesvirus from (b) into a cells,

d) replicating the AAV vector, and

e) obtaining an infectious AAV vector preparation.

23. (twice amended) A cell, which contains a recombinant herpesvirus as claimed in claim ~~30~~ 29.

24. (amended) A cell as claimed in claim 23, wherein the recombinant herpesvirus ~~or vector~~ has been introduced by infection.

29. (amended) A recombinant herpesvirus, which contains a rep and a cap gene ~~derived~~ obtained from adeno-associated viruses (AAVs) and operatively linked to an expression control sequence, with the rep gene and the cap gene being located on an insert which is integrated in the genome of the herpes virus.

30. (amended) A nucleic acid which comprises the helper functions of a herpesvirus genome which are required for replicating adeno-associated viruses (AAVs) and, inserted therein, a rep gene and a cap gene ~~derived~~ obtained from AAVs, in each case operatively linked to an expression control sequence, with the rep gene and the cap gene being located on an insert which is integrated in the genome of the herpes virus.